

# PATENT SPECIFICATION

NO DRAWINGS

Inventors: DANIEL EDWARDS, JOHN BEDFORD STENLAKE and JOHN JACOB LEWIS



**892,413**

Date of filing Complete Specification (under Section 2 (3) of the Patents Act 1949): July 7, 1958.

Application Date: July 15, 1957.

No. 22293/57.

Application Date: Dec. 31, 1957.

No. 40388/57.

Complete Specification Published: March 28, 1962.

Index at acceptance:—Class 2(3), C1E1K2, C1F1(C3: D1), C1H1(A3: B: C1), C2A(1: 5: 8: 9: 14), C2B2(A1: B2G4: B2G8: C: J), C2B3(A1: D: F: G1: G7: G8), C2B46B1, C2B47(B1: G4: G5), C2B53(A1: F: H2), C2C(1: 6D: 6E: 7A2: 7A4), C2R(18: 19: 20).

International Classification:—C07c.

## COMPLETE SPECIFICATION

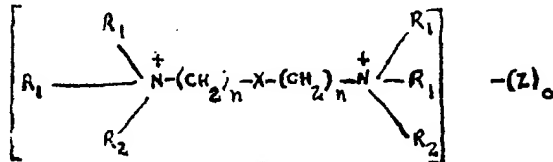
### Poly-Onium Neuromuscular Blocking Agents

We, NATIONAL RESEARCH DEVELOPMENT CORPORATION, a British Corporation, established by Statute, of 1 Tilney Street, London, W.1, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to neuromuscular

blocking agents and its objects is to provide by synthesis certain poly-onium compounds which have been tested on animals and are found to have properties by virtue of which they are suitable as such agents, acting in some respects like tubocurarine and decamethonium.

The invention comprises a poly-onium compound of the general formula



in which X represents  $\begin{array}{c} + \\ N \\ \wedge \\ R_1 \quad R_2 \end{array}$ ,  $\begin{array}{c} + \\ S \\ | \\ R_1 \end{array}$  or  $\begin{array}{c} + \\ S \\ | \\ R_2 \end{array}$

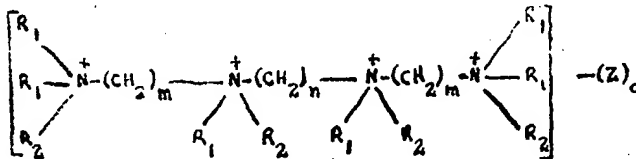
n is an integer not less than 4

Z is a non-toxic anion

o is equal to the number of onium groups in the compound divided by the valency of the anion.

20  $R_1, R_2$  represent alkyl groups and are the same or different

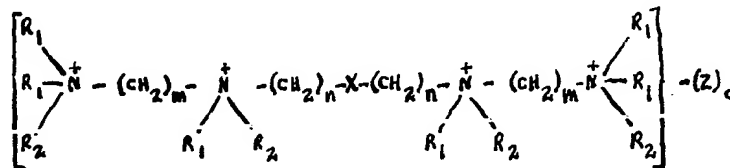
The invention also comprises a poly-onium compound of the general formula



30 in which  $R_1, R_2, n, Z$  and o are as hereinbefore defined and m is an integer not less than 4.

The invention also comprises a poly-onium compound of the general formula

500 30 001



in which  $R_1$ ,  $R_2$ ,  $Z$ ,  $X$ ,  $n$ ,  $m$  and  $o$  are as hereinbefore defined.

The anion is preferably iodine but this element as such is not critical to the activity of each compound as a blocking agent, and therefore there may be substituted any pharmaceutically equivalent anion, for example the bromide, the chloride, or the tartrate. The alkyl radical may be ethyl (Et) but it may instead be methyl (Me) or it might be propyl, isopropyl, normal butyl, secondary butyl, tertiary butyl or amyl.

Preferably  $R_1$  and  $R_2$  represent alkyl groups containing from 1 to 4 carbon atoms.

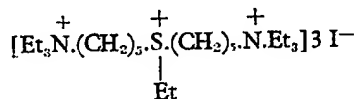
Preferably also  $m$  and  $n$  represent integers from 5 to 10.

The invention also comprises the following novel intermediate compounds formed in the preparation of the poly-onium compounds according to the invention:

- Bis-5-diethylaminopentyl sulphide.
- Bis-(6-diethylaminohexyl) ethylamine.
- Bis-(10-diethylaminodecyl) ethylamine.
- 1:20 - Bis - (diethylamino) - 7:14 - diethyl-7:14-diazaeicosane.
- 1:32 - Bis - (diethylamino) - 11:22 - diethyl - 11:22 - diazadotriacontane.
- Bis - (13 - diethylamino - 7 - ethyl - 7-azatridecyl) sulphide.
- Bis-8-diethylaminooctyl sulphide.
- Bis-(8-diethylaminooctyl) ethylamine.
- 1:28 - Bis - (diethylamino) - 11:18 - diethyl - 11:18 - diazoctacosane.
- 1:24 - Bis - (diethylamino) - 7:18 - diethyl-7:18 - diazatetracosane.

By way of illustration specific compounds representative of the series according to the foregoing general formulae and methods of preparing such compounds will now be described.

#### EXAMPLE 1.



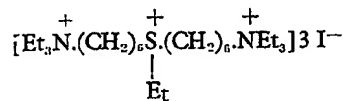
6 - Ethyl - 6 - thioniaundecylenebis (triethylammonium) triiodide was prepared from 5-hydroxypentyl-diethylamine (Synerholm, *J. Amer. Chem. Soc.* 1947, 69, 2581) through the intermediate bis-5-diethylaminopentyl sulphide as follows:

Bis-5-diethylaminopentyl Sulphide. Excess thionyl chloride (9 ml.) in benzene (20 ml.)

was slowly added to a stirred solution of 5-hydroxypentyl-diethylamine (14.3 g.) in benzene (100 ml.). The yellow crystalline mass obtained on removal of the solvent and excess reagent was dissolved in water (20 ml.), the solution cooled to 0° C, and basified with sodium hydroxide solution (30 ml.; 20%). Extraction with ether, drying ( $Na_2SO_4$ ), and evaporation of the solvent gave crude 5-chloropentyl-diethylamine (15.9 g.). The latter in ethanol (8 ml.) was slowly added to a hot solution of anhydrous sodium sulphide (4.4 g.) in water (5 ml.) and ethanol (16 ml.), and the mixture refluxed for 3 hours with continuous stirring. The residual liquid, after removal of the solvent at 100° C was poured into brine (50 ml.), and extracted with ether. The ethereal extracts were dried ( $Na_2SO_4$ ), evaporated, and the residue distilled to yield bis - 5 - diethylaminopentyl sulphide as a pale yellow oil (3.55 g., 25%), b.pt. 200—205° C/1.2 mm.  $n_D^{20}$  1.4707. Found: equiv. (titration) 157.3  $C_{18}H_{32}N_4S$  requires equivalent 158.3. Bis - 5 - diethylaminopentyl sulphide dihydrochloride (from ethanol-ether), m.pt. 155—156° C. Found: C, 55.8; H, 10.9%.  $C_{18}H_{32}N_4S \cdot 2HCl$  requires C, 55.5; H, 10.9%.

6 - Ethyl 6 - thioniaundecylenebis (triethylammonium) triiodide. Bis - 5 - diethylaminopentyl sulphide (0.85 g.) was refluxed with excess ethyl iodide (4 ml.) for not less than 40 minutes. Removal of excess reagent under reduced pressure, and recrystallisation of the product from ethanol gave 6 - ethyl - 6 - thioniaundecylenebis (triethylammonium) triiodide (1.1g) m.pt. 136.5—137.5° C. Found: I, 48.3; N, 3.5%  $C_{24}H_{48}N_6S \cdot 3I_3$  requires I, 48.5; N, 3.6%.

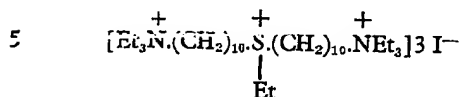
#### EXAMPLE 2.



7 - Ethyl - 7 - thioniatridecylenebis (triethylammonium) triiodide was prepared from bis-6 - diethylaminohexyl sulphide (Edwards and Stenlake, *J. Pharm. Pharmacol.*, 1955, 7, 852) (1.64 g.) by refluxing with ethyl iodide (3 ml.) for 25 mins. Removal of excess reagent under reduced pressure and recrystallisation of the product from ethanol gave almost colourless crystals (2.95 g., 76.3%) of 7-ethyl-7-thionia-

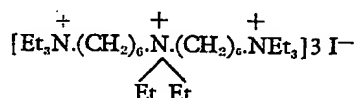
tridecylenebis (triethylammonium) triiodide, m.pt. 142—143° C. Found: N, 3.7; I, 46.6%  $C_{26}H_{54}N_2SI_3$  requires N, 3.5; I, 46.9%

## EXAMPLE 3.



11 - Ethyl - 11 - thionaheneicosylenebis (triethylammonium) triiodide was prepared from bis - 10 - diethylaminodecyl sulphide (1.1g.) (Edwards and Stenlake, *J. Pharm. Pharmacol.*, 1955, 7, 852) by refluxing with ethyl iodide (2 ml.) and ethanol (1 ml.) for 45 minutes. Evaporation to dryness under reduced pressure yielded 11 - ethyl - 11 - thionaheneicosylenebis (triethylammonium) triiodide (0.6 g., 27%) m.p. 123.5—124° C. (from acetone-ether). Found: N, 3.0; H, 41.2%  $C_{33}H_{76}N_2SI_3$  requires, N, 3.0; I, 41.2%.

## EXAMPLE 4.



20 7:7 - Diethyl - 7 - azoniatridecylenebis (triethylammonium) triiodide was prepared from 6 - hydroxyhexyldiethylamine (Work, *J. Chem. Soc.*, 1942, 426; Edwards and Stenlake, *J. Pharm. Pharmacol.*, 1955, 7, 852), through the intermediates 6 - bromohexyldiethylamine, 6-diethylaminohexylethylamine and bis(6-diethylaminohexylethylamine) as follows:

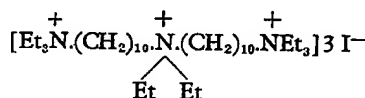
25 6 - Bromohexyldiethylamine. 6-Hydroxyhexyldiethylamine (35.2 g.) was refluxed with 48% hydrobromic acid (95 ml.) and concentrated sulphuric acid (33 ml.) for 4 hours. The cooled solution, diluted with water (1 l.) was basified with sodium carbonate, and extracted with chloroform. Evaporation of the solvent under reduced pressure at 17° C., and filtration of solid matter from the oily residue gave 6-bromohexyldiethylamine as a reddish brown oil containing traces of chloroform, which was used immediately in the next stage.

30 6 - Diethylaminohexylethylamine. Crude 6-bromohexyldiethylamine and excess ethylamine (40 ml.) were refluxed for 2 hours. Evaporation of the chloroform and excess ethylamine yielded a damp crystalline residue which was basified and extracted with ether. Evaporation of the ether yielded an oil (24.8 g.) which on distillation gave 6 - diethylaminohexylethylamine, b.p. 86—89° C./0.55 mm.  $n_D^{17}$  1.4493, (21.5 g., 53%). Dihydrochloride (from ethanol-ether), m.p. 172—173° C. Found: C, 51.8; H, 10.6; Cl, 25.8%.  $C_{12}H_{28}N_2Cl_2$  requires C, 52.7; H, 11.1; Cl, 25.9%.

Bis - (6 - diethylaminohexylethylamine. 6-Diethylaminohexylethylamine (Work, *J. Chem. Soc.*, 1942, 426; Edwards and Stenlake, *J. Pharm. Pharmacol.*, 1955, 7, 852) (6.3 g.) in xylene (20 ml.) for 5 hours. On cooling the reaction mixture was extracted with dilute hydrochloric acid (10%) and the latter basified and extracted with benzene. Evaporation of the solvent and fractional distillation of the residue gave bis - (6 - diethylaminohexylethylamine, as a pale yellow oil, b.p. 165—168° C./0.7 mm,  $n_D^{18}$  1.4610 (2.2 g., 19%). Found: C, 74.7; H, 13.1 per cent.  $C_{22}H_{44}N_2$  requires C, 74.3; H, 13.1 per cent.

7:7 - Diethyl - 7 - azoniatridecylenebis (triethylammonium) triiodide. Bis - (6 - diethylaminohexylethylamine (0.57 g.) was refluxed with ethyl iodide (3 ml.) for 15 minutes. Evaporation of excess ethyl iodide yielded 7:7 - Diethyl - 7 - azoniatridecylenebis (triethylammonium) triiodide (1.02 g., 77%), m.p. 261—262° C. (from ethanol). Found: N, 4.95; I, 46.2%.  $C_{28}H_{64}N_3I_3$  requires N, 5.1; I, 46.2%.

## EXAMPLE 5.



11:11 - Diethyl - 11 - azoniatheneicosylenebis (triethylammonium) triiodide was prepared from 10-Hydroxydecyldiethylamine (Schinzel and Benoit, *Bull. Soc., Chim. Fr.*, 1939, [5], 6, 501; Edwards and Stenlake, *J. Pharm. Pharmacol.*, 1955, 7, 852) through the intermediate 10-bromodecyldiethylamine, 10-diethylaminodecylethylamine and bis(10-diethylaminodecylethylamine) as follows:

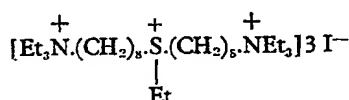
10 - Diethylaminodecylethylamine 10-from 10-hydroxydecyldiethylamine (20.1 g.) by the method described for 6-bromohexyldiethylamine, and was obtained as a colourless oil, bp. 130° C/0.5 mm.,  $n_D^{14}$  1.4714 (21.4 g., 84%). Found: Equiv. (titration) 294.3; Br, 27.25 per cent.  $C_{11}H_{24}NBr$  requires equiv. 292.3; Br, 27.3 per cent.

10 - Diethylaminodecylethylamine 10-Bromodecyldiethylamine (20.9 g.) and excess ethylamine (60ml.) were refluxed for 2 hours. Distillation of the excess ethylamine, addition of water to the residue and extraction with benzene yielded an oily product which on distillation gave 10-diethylaminodecylethylamine b.p. 133—135° C/0.8 mm. (14 g.),  $n_D^{19}$  1.4535, together with bis - (10 - diethylaminodecylethylamine, b.p. 216—217° C./0.75 mm. (0.9 g.). 10 - Diethylaminodecylethylamine Dihydrochloride (from ethanol-ether), m.p. 147—148° C. Found: C, 58.1; H, 11.4; Cl, 20.3 per cent.  $C_{11}H_{23}N_2Cl_2$  requires C, 58.3; H, 11.6; Cl, 21.5 per cent.

Bis - (10 - diethylaminodecyl) ethylamine. 10 - Bromodecyldiethylamine (9 g.) in chloroform (10 ml.) was added slowly (40 minutes) to a refluxing solution of 10-diethylaminodecyldiethylamine (7.9 g.) in chloroform (15 ml.), and the mixture refluxed for a further 30 minutes. On evaporation the residue was basified and extracted with benzene. After removal of solvent, and fractional distillation of the residual oil, bis - (10 - diethylaminodecyl) ethylamine was obtained as a pale yellow oil, b.p. 212—216° C./0.25 mm. (3.8 g.)  $n_D^{21}$  1.4660.

11:11 - Diethyl - 11 - azoniaheicosylenebis (triethylammonium) Triiodide. Bis - (10 - diethylaminodecyl) ethylamine (0.93 g.) was refluxed with ethyl iodide (2 ml.) and ethanol (1 ml.) for 50 minutes. Evaporation to dryness under reduced pressure yielded 11:11-diethyl - 11 - azoniaheicosylenebis (triethylammonium) triiodide (1.7 g.), m.p. 204° C (from acetone-ether). Found: C, 46.1; H, 8.2; N, 4.4; I, 40.5%;  $C_{36}H_{70}N_3I_3$  requires C, 46.2; H, 8.7; N, 4.5; I, 40.7%.

#### EXAMPLE 6.



9 - Ethyl - 9 - thioniaheptadecylenebis - (triethylammonium) Triiodide was prepared from 6 - chlorohexyl - diethylamine through the intermediate bis - 8 - diethylaminooctyl sulphide as follows:—

1:1 - Bisethoxycarbonyl - 7 - diethylaminoheptane was prepared from 6 - chlorohexyldiethylamine (44 g) by the method used in the preparation of 1:1 - bisethoxycarbonyl - 4-diethylaminobutane (Edwards, Lewis, Stenlake, and Zona, *J. Pharm. Pharmacol.*, 1957, 9, 1004), with the modification that 10% excess sodiummalonic ester was used, and reflux time was increased to 4 hours. 1:1-Bisethoxycarbonyl - 7 - diethylaminoheptane was obtained as a pale yellow oil, b.p. 147—155° C./0.8 mm.,  $n_D^{15.5}$  1.4472 (34.5 g., 47.65%) and used without characterisation in the next stage of the reaction.

Ethyl - 8 - diethylaminocaprylate was prepared from 1:1 - bisethoxycarbonyl - 7 - diethylaminoheptane (45.2 g) by the method used for the preparation of ethyl-5-diethylaminovalerate (Edwards, Lewis, Stenlake and Zoha, *J. Pharm. Pharmacol.*, 1957, 9, 1004), with the modification that the initial reflux time with hydrochloric acid was increased to 4 hours. Ethyl 8-diethylaminocaprylate obtained as a colourless oil, b.p. 111—114° C./0.65 mm.,  $n_D^{15}$  1.4428 (21.5g., 62%) was characterised as 7-ethoxycarbonylheptyl triethylammonium iodide (prepared by the action of ethyl iodide), m.p. 64.5—65.5° C. (from

acetone-ether). Found: N, 3.6; I, 32.1 per cent.  $C_{16}H_{34}NO_2I$  requires N, 3.5; I, 32.25 per cent.

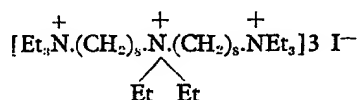
8-Hydroxyoctyldiethylamine. Ethyl 8-diethylaminocaprylate (35.4 g) was reduced with lithium aluminium hydride by the method used for the preparation of 5-hydroxypentyldiethylamine (Edwards, Lewis, Stenlake and Zoha, *J. Pharm. Pharmacol.*, 1957, 9, 1004) to yield 8-hydroxyoctyldiethylamine as a colourless oil b.p. 114—117° C./0.7mm.,  $n_D^{16.5}$  1.5490 (26.2 g., 90%). Hydrochloride (from ethanol-ether), m.p. 90—91° C. Found: C, 60.4; H, 11.3; Cl, 15.0 per cent.  $C_{12}H_{25}ONCl$  requires C, 60.6; H, 11.9; Cl, 14.9 per cent.

8-Chlorooctyldiethylamine was prepared from 8-hydroxyoctyldiethylamine (8.6g) by the method described for the preparation of 6-chlorohexyldiethylamine (Edwards and Stenlake, *J. Pharm. Pharmacol.*, 1955, 7, 852). 8-chlorooctyldiethylamine was obtained as a colourless oil, b.p. 94—96° C./0.55 mm.,  $n_D^{17}$  1.4550 (9.1g., 96%). (Altman, *Rec. trav. chim.*, 1938, 57, 941).

Bis - 8 - diethylaminooctyl sulphide was prepared from 8-chlorooctyldiethylamine (9g.) by the method described for the preparation of bis - 5 - diethylaminopentyl sulphide. Bis-8 - diethylaminooctyl sulphide was obtained as a straw-coloured liquid, b.p. 210—212° C./0.65 mm.,  $n_D^{16.5}$  1.4768 (5.9g., 72%). Found: Equiv. (titration) 203.5  $C_{24}H_{52}N_2S$  requires equiv. 200.4. Dihydrochloride (from ethanol), m.p. 145° C. Found: C, 60.85; H, 11.0 per cent.  $C_{24}H_{52}N_2S \cdot 2HCl$  requires C, 60.85; H, 11.5 per cent.

9 - Ethyl - 9 - thioniaheptadecylenebis (triethylammonium) triiodide was prepared from bis - 8 - diethylaminooctyl sulphide (0.63g.) by refluxing with ethyl iodide (4 ml) for 15 minutes. Removal of excess reagent under reduced pressure yielded 9 - ethyl - 9 - thioniaheptadecylenebis (triethylammonium) triiodide (0.64g.) (from ethanol-ether), m.p. 159—160° C. (decomp.). Found: N, 3.2; I, 43.0 per cent,  $C_{34}H_{68}N_3SI_3$  requires N, 3.2; I, 43.8 per cent.

#### EXAMPLE 7.



9:9 - Diethyl - 9 - azoniaheptadecylenebis (triethylammonium) Triiodide was prepared from 8-hydroxyoctyldiethylamine through the intermediate 8 - bromooctyldiethylamine, 8-diethylaminooctylethylamine and bis - (8 - diethylaminooctyl) ethylamine as follows:

8 - Bromooctyldiethylamine was prepared from 8 - hydroxyoctyldiethylamine (8.6g) by the method described for 6 - bromohexyldiethylamine, and was obtained as a golden brown oil (10.3g., 91.2%)  $n_D^{17}$  1.4695, which

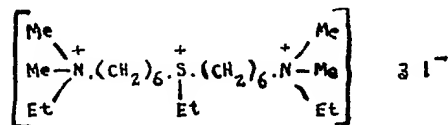
was not further purified.

- 8 - *Diethylaminooctylethylamine* was prepared from 8-bromooctyldiethylamine (10.3g) by the method described for 10-diethylaminodecylethylamine, and was obtained as a colourless oil, b.p. 104°—106° C./0.7 mm.,  $n_D^{17.5}$  1.4530 (7.4g., 83%). *Dihydrochloride* (from ethanol-ether), m.p. 159.5—160.5° C. (hygroscopic). Found: N, 9.2; Cl, 23.0 per cent.
- 10  $C_{14}H_{34}N_2Cl_2$  requires N, 9.3; Cl, 23.5 per cent.

- Bis - (8 - diethylaminooctyl) ethylamine* was prepared from 8-diethylaminooctylethylamine (6.95g) and 8-chlorooctyldiethylamine (6.7g) by the method described for the preparation of bis - (6 - diethylaminoethyl) ethylamine. Bis - (8-diethylaminooctyl) ethylamine was obtained as a yellow oil, b.p. 230—250° C. (bath)/0.8 mm.,  $n_D^{17}$  1.4642 (2.3g; 18%). *Trihydrochloride* (from acetone-ether), m.p. 165—166° C. (decomp.). Found: Cl, 20.9 per cent.  $C_{22}H_{46}N_3Cl_3$  requires Cl, 20.4 per cent.

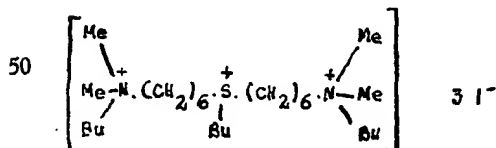
- 9:9 - *Diethyl - 9 - azoniaheptadecylenebis (triethylammonium) triiodide* was prepared from bis - (8 - diethylaminooctyl) ethylamine (0.56g) by refluxing with ethyl iodide (2 ml) and ethanol (2 ml) for 15 minutes. On evaporation under reduced pressure 9:9 - *diethyl - 9 - azoniaheptadecylenebis (triethylammonium) triiodide* was obtained (from ethanol), m.p. 251—252° C. (decomp.). Found: C, 43.2; H, 8.1; I, 43.0 per cent.  $C_{30}H_{72}N_3I_3$  requires C, 43.7; H, 8.25; I, 43.3 per cent.

#### EXAMPLE 8.



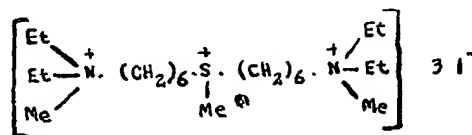
- 7 - *Ethyl - 7 - thioniatridecylenebis - (dimethylethylammonium) triiodide* was prepared from bis - 6 - dimethylaminoethyl sulphide (0.63g) (Edwards, Lewis, Stenlake and Zoha, *J. Pharm. Pharmacol.*, 1957, 9, 1004) by refluxing with ethyl iodide (2 ml.) and ethanol (2 ml.) for 35 minutes. Evaporation under reduced pressure yielded 7 - *ethyl - 7 - thioniatridecylenebis - (dimethylethylammonium) triiodide*, (1 g.) m.p. 137—137.5° C. (from ethanol). Found: N, 3.6; I, 50.1%  $C_{22}H_{51}N_2SI_3$  requires N, 3.7; I, 50.3%.

#### EXAMPLE 9.



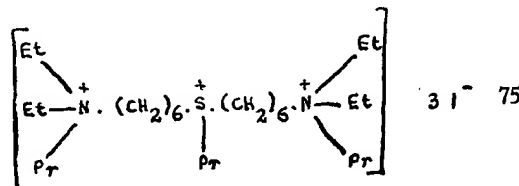
- 7 - *n - Butyl - 7 - thioniatridecylenebis (dimethyl - n - butylammonium) Triiodide* was prepared from bis - 6 - dimethylaminoethyl sulphide (0.61 g.) by refluxing with *n*-butyl iodide for 40 minutes. Evaporation under reduced pressure yielded 7 - *n - butyl - 7 - thioniatridecylenebis - (dimethyl - n - butylammonium) triiodide* (from alcohol-acetone-ether) (0.9 g.) m.p. 151—151.5° C. Found: N, 3.4; I, 45.35%  $C_{28}H_{63}N_2SI_3$  requires N, 3.3; I, 45.3%.

#### EXAMPLE 10.



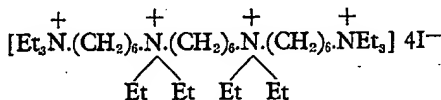
- 7 - *Methyl - 7 - thioniatridecylenebis - (diethylmethylammonium) Triiodide* was prepared from bis - 6 - diethylaminoethyl sulphide (0.81g.) by refluxing with methyl iodide (2 ml.) and ethanol (2 ml.) for 20 minutes. Evaporation under reduced pressure yielded 7 - *methyl - 7 - thioniatridecylenebis - (diethylmethylammonium) triiodide* (1.7 g.), m.p. 135—136° C. (from ethanol). Found N, 3.6; I, 49.6%.  $C_{23}H_{53}N_2SI_3$  requires N, 3.6; I, 49.4%.

#### EXAMPLE 11.



- 7 - *n - Propyl - 7 - thioniatridecylenebis - (diethyl - n - propylammonium) Triiodide* was prepared from bis - 6 - diethylaminoethyl sulphide (0.78g.) by refluxing with *n*-propyl iodide (2 ml.) and ethanol (2 ml.) for 45 minutes. Evaporation under reduced pressure yielded 7 - *n - propyl - 7 - thioniatridecylenebis - (diethyl - n - propylammonium) triiodide* (1.g.), m.p. 125.5—126° C. (from ethanol-ether). Found: N, 3.3; I, 44.3%  $C_{29}H_{65}N_2SI_3$  requires N, 3.3; I, 44.5%.

#### EXAMPLE 12.



## METHOD 1.

7:7:14:14 - Tetraethyl - 7:14 - diazo-  
niaeicosylenebis (triethylammonium) tetra-  
iodide was prepared from adipoyl chloride and  
6 - diethylaminohexyl - ethylamine (Edwards  
and Stenlake, *J. Pharm. Pharmacol.* 1955, 7,  
852) as follows:—

1:20 - Bis - (diethylamino) - 7:14 - diethyl-  
7:14 - diazaeicosane. Adipic acid (2.54 g.)  
was refluxed with excess thionyl chloride for  
1½ hours. After removal of excess reagent, the  
acid chloride was heated in benzene (50 ml.)  
over a water bath, and an excess of 6-diethyl-  
aminohexylethylamine (14.2 g.) in benzene (50  
ml.) added with stirring (10 minutes). The  
mixture was then refluxed gently for 10  
minutes, cooled and extracted with 10%  
hydrochloric acid. The latter solution was  
basified and extracted with benzene. After  
removal of solvent, the bulk of the 6-diethyl-  
aminohexylethylamine was distilled leaving the  
crude N,N' - diethyl - N,N' - bis(6 - diethyl-  
aminohexyl) - adipamide. Lithium aluminium  
hydride reduction of this amide in ether, and  
distillation of the residual oil yielded 1:20-  
bis - (diethylamino) - 7:14 - diethyl - 7:14-  
diazaeicosane as a yellow oil (1.15 g., 13%),  
n<sub>D</sub><sup>20</sup> 1.4695, b.p. 227—229° C./0.6 mm.

7:7:14:14 - Tetraethyl - 7:14 - diazo-  
niaeicosylenebis (triethylammonium) tetra-  
iodide. 1:20 - Bis - diethylamino - 7:14-  
diethyl - 7:14 - diazaeicosane (1.1 g.), ethyl  
iodide (3 ml.), and ethanol (3 ml.) were  
refluxed for 20 minutes. Evaporation under  
reduced pressure and recrystallisation from  
ethanol yielded 7:7:14:14 - tetraethyl-  
7:14 - diazaeicosylenebis (triethylammo-  
nium) tetraiodide (1.1 g., 46.2%), m.p. 248.5°  
—249° C. Found: N, 4.9; I, 45.9 per cent.  
C<sub>33</sub>H<sub>56</sub>N<sub>4</sub>I<sub>4</sub> requires N, 5.1; I, 45.9 per cent.

## METHOD 2.

7:7:14:14 - Tetraethyl - 7:14 - diazo-  
niaeicosylenebis (triethylammonium) tetra-  
iodide was prepared from N,N - diethyladip-  
amoyl chloride and NN' - diethylhexa-

methylenediamine (Wittbecker et al, *J. Amer.  
Chem. Soc.* 1947, 69, 579) as follows:—

N,N - Diethyladipamic acid. Ethyl N,N-  
diethyladipamate (100 g.) was refluxed for  
30 minutes with a slight excess (1100 ml.) of

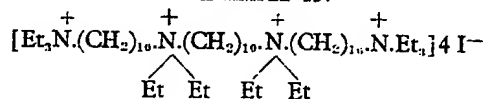
ethanolic potassium hydroxide (0.8664 —) and

the bulk of the ethanol removed by dis-  
tillation. To the residual liquid was added  
with stirring hydrochloric acid (50 ml.) and  
water (50 ml.), and the mixture extracted with  
benzene, washed with brine and dried  
(Na<sub>2</sub>SO<sub>4</sub>). After removal of solvent, distilla-  
tion of the residual oil yielded N,N - diethyl-  
adipamic acid as a yellow viscous oil (83.96 g.;  
95.7%), n<sub>D</sub><sup>20</sup> 1.4733. B. P. 182° C./0.5mm.  
Found: Equiv. (titration) 201.9, C<sub>16</sub>H<sub>19</sub>NO<sub>4</sub>  
requires equiv. 201.3.

1:20 - Bis - (diethylamino) - 7:14 - diethyl-  
7:14 - diazaeicosane. N,N - Diethyladipamic  
acid (17.4 g.) in benzene (7 ml.) was refluxed  
with excess thionyl chloride (8 ml.) for 5  
minutes. After removal of solvent and excess  
reagent the acid chloride in benzene (25 ml.)  
was added with stirring (25 minutes) to a solu-  
tion of NN' - diethylhexamethylenediamine  
(7.5 g.) in benzene (40 ml.). The mixture was  
then refluxed gently for 20 minutes, cooled,  
extracted with 10% hydrochloric acid, the  
latter solution basified and extracted with ben-  
zene. Removal of solvent yielded crude bis-  
(N - ethyl - N',N' - diethyladipamoyl) hexa-  
methylenediamine. Lithium aluminium hydride  
reduction of this amide and distillation of the  
residual oil yielded 1:20 - bis - (diethyl-  
amino) - 7:14 - diethyl - 7:14 - diazaeico-  
sane as a yellow oil (6 g., 28.75%), n<sub>D</sub><sup>22</sup> 1.4665,  
b.p. 227—229° C./0.6 mm. Tetrachloride  
(from ethanol-ether), m.p. 249—250° C  
(decomp.) Found: N, 8.98; Cl, 22.3 per cent  
C<sub>33</sub>H<sub>56</sub>N<sub>4</sub>Cl<sub>4</sub> requires Cl, 22.5 per cent; N 8.9  
per cent.

7:7:14:14 - Tetraethyl - 7:14-diazenaei-  
cosylenebis (triethylammonium) tetraiodide.  
As in method 1.

## EXAMPLE 13.



11:11:22:22 - Tetraethyl - 11:22 - diazo-  
niadotriacontylenebis (triethylammonium)  
tetraiodide was prepared from sebacyl  
chloride and 10 - diethylaminodecylethylamine  
as follows:—

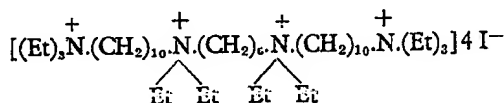
1:32 - Bis - (diethylamino) - 11:22 - di-  
ethyl - 11:22 - diazadotriacontane was pre-  
pared from sebacic acid (2.53 g.) and 10-  
diethylaminodecylethylamine (13.1 g.) as des-  
cribed for 1:20 - bis - (diethylamino) - 7:14-  
diethyl - 7:14 - diazaeicosane, and was  
obtained as a yellow oil, b.p. 360—380° C

(bath)/0.7 mm. (4.46 g.; 55%) n<sub>D</sub><sup>18</sup> 1.4692,  
Found: Equiv. (Titration) 165.5 C<sub>42</sub>H<sub>80</sub>N<sub>4</sub>  
requires equiv. 162.8.

11:11:22:22 - Tetraethyl - 11:22 - diazo-  
niadotriacontylenebis (triethylammonium)  
tetraiodide. 1:32 - Bis - (diethylamino)-  
11:22 - diethyl - 11:22 - diazoniadotriacon-  
tane (0.95 g.) was refluxed with ethyl iodide (3  
ml.) and ethanol (3 ml.) for 50 minutes.  
Evaporation under reduced pressure and  
recrystallisation from acetone-ether gave  
11:11:22:22 - tetraethyl - 11:22 - diazo- 115

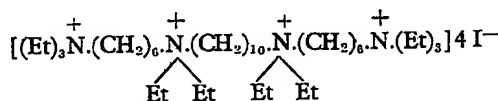
*niadotriacontylenebis* (triethylammonium) cent.  $C_{70}H_{110}I_4N_4$  requires C, 47.1; H, 8.7; 5  
*tetraiodide*. m.p. 186—187° C (1.4 g.; I, 39.8 per cent.  
 75.3%) Found: C, 46.8; H, 8.5; I, 39.4 per

## EXAMPLE 14



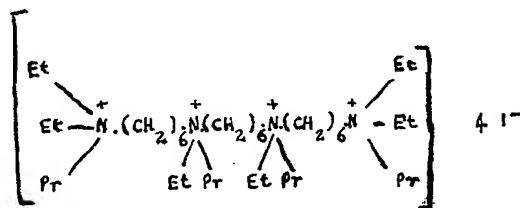
- 11:11:18:18 - Tetraethyl - 11:18 - diazo-  
 nioctacosylenebis (triethylammonium) Tetra-  
 iodide was prepared from adipoyl chloride and  
 10 - diethylaminodecylethylamine as follows:  
 1:28 - Bis - (diethylamino) - 11:18 - di-  
 ethyl - 11:18 - diazoctacosane was prepared  
 from adipic acid (2.61 g.) and 10-diethyl-  
 aminodecylethylamine (18.46 g.) as described  
 for 1:20 - bis - (diethylamino) - 7:14 - di-  
 ethyl - 7:14 - diazaicosane, and was obtained  
 as a yellow oil, b.p. 300—310° C. (bath)/0.6  
 mm. (6.74 g., 63.4%),  $n_D^{20}$  1.4679. Found:  
 20 Equiv. 150.2.  $C_{38}H_{52}N_4$  requires Equiv. 148.8.  
*Tetrahydrochloride* m.p. 161.5—162.5° C  
 (from ethanol-ether). Found: N, 7.5; Cl 19.2
- per cent.  $C_{38}H_{52}N_4I_4$  requires N, 7.6; Cl,  
 19.15 per cent.  
 11:11:18:18 - Tetraethyl - 11:18 - diazo-  
 nioctacosylenebis (triethylammonium) Tetra-  
 iodide. 1:28 - Bis - (diethylamino) - 11:18-  
 diethyl-11:18-diazoctacosane (0.52 g.) was  
 refluxed with ethyl iodide (2 ml.) and ethanol  
 (3 ml.) for 30 minutes. Evaporation under  
 reduced pressure and recrystallisation from  
 ethanol yielded 11:11:18:18 - tetraethyl-  
 11:18 - diazonioctacosylenebis (triethyl-  
 ammonium) tetraiodide (1.1 g.), m.p. 221—  
 221.5° C. Found: N, 4.7; I, 41.6 per cent.  
 35  $C_{38}H_{52}N_4I_4$  requires N, 4.6; I, 41.6 per cent.

## EXAMPLE 15



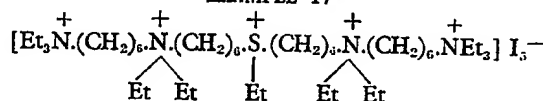
- 7:7:18:18 - Tetraethyl - 7:18 - diazoia-  
 tetracosylenebis (triethyl - ammonium) Tetra-  
 iodide was prepared from sebacoyl chloride and  
 6-diethylaminohexylethylamine as follows:—  
 1:24 - Bis - (diethylamino) - 7:18 - di-  
 ethyl - 7:18 - diazatetracosane was prepared  
 from sebacic acid (5.27 g.) and 6-diethylamino-  
 hexylethylamine (25.4 g.) as described for  
 (1:20 - bis - (diethylamino) - 7:14 - diethyl-  
 7:14 - diazaicosane, and was obtained as a  
 pale yellow oil, b.p. 280—290° C. (bath)/0.6  
 mm. (8.15 g., 58%),  $n_D^{20}$  1.4673. Found:  
 50 Equiv. 135.9.  $C_{34}H_{48}N_4$  requires Equiv. 134.8.  
*Tetrahydrochloride*, m.p. 196—197° C (from  
 ethanol-ether). Found: N, 8.1; Cl, 20.3 per
- cent,  $C_{34}H_{48}N_4Cl_4$  require N, 8.2; Cl, 20.7 per  
 cent.  
 7:18:7:18 - Tetraethyl - 7:18 - diazoia-  
 tetracosylenebis (triethylammonium) Tetra-  
 iodide. 1:24 - Bis - (diethylamino) - 7:18-  
 diethyl - 7:18 - diazatetracosane (0.4 g.) was  
 refluxed with ethyliodide (2 ml.) and ethanol  
 (2 ml.) for 30 minutes. Evaporation under  
 reduced pressure and recrystallisation from  
 ethanol gave 7:7:18:18 - tetraethyl - 7:18-  
 diazoniatetracosylenebis (triethylammonium)  
 tetraiodide (0.98 g.) m.p. 167.5—168.5° C.  
 65 Found: N, 4.7; I, 43.2%.  $C_{42}H_{54}N_4I_4$   
 requires N, 4.8; I, 43.6%.

## EXAMPLE 16



- 70 7:14 - Diethyl - 7:14 - di - n - propyl-  
 7:14 - diazonaeicosylenebis (diethyl - n -  
 propylammonium) Tetraiodide was prepared  
 from 1:20 - bis - (diethylamino) - 7:14-  
 diethyl - 7:14 - diazonaeicosane (0.64 g.) by  
 75 refluxing with n-propyl iodide (2 ml.) and  
 ethanol (2 ml.) for 50 minutes. Evaporation
- under reduced pressure yielded 7:14-diethyl-  
 7:14 - di - n - propyl - 7:14 - diazonaeico-  
 sylenebis (diethyl - n - propylammonium)  
 tetraiodide (1.4 g.) m.p. 197.5—198.5° C  
 (decomp.). Found: N, 4.9; I, 43.7 per cent.  
 80  $C_{42}H_{54}N_4I_4$  requires N, 4.8; I, 43.6 per cent.

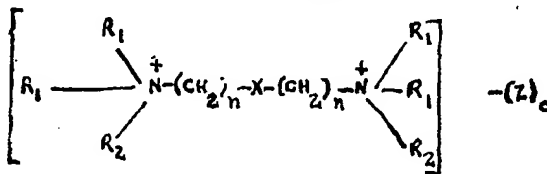
## EXAMPLE 17



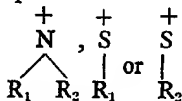
- 7:7:14:21:21 - Pentaethyl - 7:21 - diazonia-  
14 - thioniaheptacosylenebis (triethylammonium) pentaiodide was prepared from ethyl  
5 hydrogen adipate and 6 - diethylaminoethyl  
ethylamine as follows:—  
Ethyl N - ethyl - N - (6 - diethylamino-  
hexyl) - adipamate. Ethyl adipoyl chloride,  
10 prepared by refluxing ethyl hydrogen adipate  
(52 g.) with thionyl chloride in the usual way,  
was dissolved in benzene (100 ml.). 6 - Di-  
ethylaminoethylamine (58.93 g.) in ben-  
zene (25 ml.) was added slowly (45 mins.) with  
15 stirring, and the mixture refluxed gently for  
30 minutes. After extraction with 10% hydro-  
chloric acid, basifying and extraction with  
ether, fractional distillation yielded ethyl N-  
ethyl - N - (6 - diethylaminoethyl) - adip-  
20 amate as a yellow oil; b.p. 199—201° C./0.55  
mm.,  $n_D^{21.5}$  1.4648 (45.25 g., 43.2%). Found:  
Equiv. 354.6.  $\text{C}_{26}\text{H}_{44}\text{N}_2\text{O}_3$  requires Equiv.  
356.5.  
13 - Diethylamino - 7 - ethyl - 7 - azatri-  
25 decan - 1 - ol. Ethyl N - ethyl - N - (6-  
diethylaminoethyl) - adipamate (35.46 g.) in  
dry ether (150 ml.) was added to a stirred  
and refluxing suspension of lithium aluminium  
hydride (7 g.) in dry ether (600 ml.) at a rate  
30 sufficient just to maintain refluxing. The  
reaction mixture was cooled, and water added  
dropwise to decompose the excess lithium  
hydride, and then excess water added. The  
35 ethereal layer was decanted and the residue  
washed with ether. The combined ethereal  
solutions, were dried ( $\text{Na}_2\text{SO}_4$ ) evaporated and  
the residue distilled to yield 13 - diethylamino-  
7 - ethyl - 7 - azatridecan - 1 - ol, as a colour-  
less oil, b.p. 170—175° C./0.55 mm.,  $n_D^{21}$   
40 1.4673 (21 g., 70.3%). Found: Equiv. 149.4.  
 $\text{C}_{18}\text{H}_{34}\text{ON}_2$  requires Equiv. 150.3. Dihydro-  
chloride (from ethanol-ether), m.p. about  
155° C. Found: Cl, 19.0 per cent.  
 $\text{C}_{18}\text{H}_{32}\text{ON}_2\text{Cl}_2$  requires Cl, 19.0 per cent.  
45 13 - Diethylamino - 7 - ethyl - 7 - azatri-  
decyl Chloride 13 - Diethylamino - 7 - ethyl-  
7 - azatridecan - 1 - ol (19 g.) in benzene (60  
ml.) was treated with thionyl chloride (8 ml.)  
in benzene (20 ml.) The crystalline mass  
obtained on removal of the solvent and excess  
50 reagent was dissolved in water (10 ml.), the  
solution cooled to 0° and basified with sodium  
hydroxide solution. Extraction with ether, dry-  
ing ( $\text{Na}_2\text{SO}_4$ ), evaporation of the solvent and  
distillation gave 13 - diethylamino - 7 - ethyl-  
55 7 - azatridecyl chloride as a pale yellow oil,  
b.p. 167—169° C./0.7 mm.  $n_D^{21}$  1.4648  
(13.55 g., 67.1%). Found: Equiv. 158.5  
 $\text{C}_{14}\text{H}_{28}\text{N}_2\text{Cl}$  requires Equiv. 159.5 Dihydro-  
chloride (from ethanol-ether), m.p. 151.5—  
60 152.5° C.  
Bis - (13 - diethylamino - 7 - ethyl - 7-  
azatridecyl) Sulphide was prepared from 13-  
diethylamino - 7 - ethyl - 7 - azatridecyl  
chloride (13.33 g.) and anhydrous sodium sul-  
phide as described for bis - 5 - diethylamino-  
65 pentyl sulphide (Edwards, Lewis, Stenlake and  
Zoha, *J. Pharm. Pharmacol.*, 1957, 9, 1004).  
Bis - (13 - diethylamino - 7 - ethyl - 7 - aza-  
tridecyl) sulphide was obtained as a yellow  
oil, b.p. 305—315° C. (bath)/0.5 mm,  $n_D^{24}$   
70 1.4780, (8.67 g., 69%). Found: Equiv. 150.5.  
 $\text{C}_{36}\text{H}_{76}\text{N}_4\text{S}$  requires 149.8 Tetrahydrochloride  
(from ethanol-ether), m.p. 173—174° C  
(decomp.). Found: N, 7.5 per cent.  
 $\text{C}_{36}\text{H}_{72}\text{N}_4\text{S}_4\text{Cl}_4$  requires N, 7.5 per cent.  
7:7:14:21:21 - Pentaethyl - 7:21-  
diazonia - 14 - thioniaheptacosylenebis (tri-  
ethylammonium) pentaiodide. Bis - (13 - di-  
ethylamino - 7 - ethyl - 7 - azatridecyl) sul-  
phide (2.1 g.) was refluxed with ethyl iodide (3  
80 ml.) and ethanol (3 ml.) for 35 minutes.  
Evaporation under reduced pressure and re-  
crystallisation of the product from acetone-  
ether yielded 7:7:14:21:21 - pentaethyl-  
7:21 - diazonia - 14 - thioniaheptacosylenebis  
85 (triethylammonium) pentaiodide, m.p. 165.5—  
166.5° C (decomp.) (3g.; 62%) Found: I,  
46.2, N, 4.2 per cent.  $\text{C}_{36}\text{H}_{102}\text{I}_5\text{N}_5$  requires  
I, 46.0, N, 4.1 per cent.

## WHAT WE CLAIM IS:—

1. A poly-onium compound of the general  
formula



in which X represents



$R_1, R_2$  represent alkyl groups and are the same

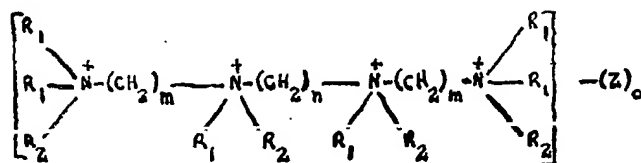
or different

$n$  is an integer not less than 4

$Z$  is a non-toxic anion

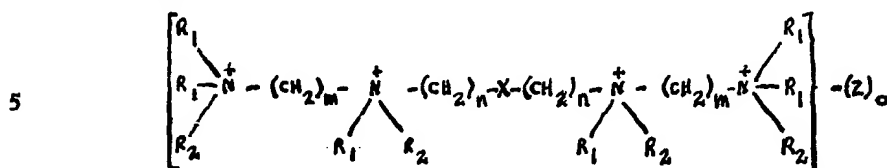
$O$  is equal to the number of onium groups in  
the compound divided by the valency of  
the anion.

## 2. A poly-onium of the general formula



in which  $R_1$ ,  $R_2$ ,  $n$ ,  $Z$  and  $o$  are as hereinbefore defined and  $m$  is an integer not less than 4.

## 3. A poly-onium compound of the general formula



in which  $R_1$ ,  $R_2$ ,  $Z$ ,  $X$ ,  $n$ ,  $m$  and  $o$  are as hereinbefore defined.

4. A compound according to any of claims 1 to 3 in which  $R_1$  and  $R_2$  represent alkyl groups containing from 1 to 4 carbon atoms.

5. A compound according to any of claims 1 to 4 in which  $m$  and  $n$  represent integers from 5 to 10.

6. 6 - Ethyl - 6 - thioniaundecylenebis (triethylammonium) triiodide.

7. 7 - Ethyl - 7 - thioniatridecylenebis (triethylammonium) triiodide.

8. 11 - Ethyl - 11 - thioniaheneicosylenebis (triethylammonium) triiodide.

9. 7:7 - Diethyl - 7 - azoniatridecylenebis (triethylammonium) triiodide.

10. 11:11 - Diethyl - 11 - azoniaheneicosylenebis (triethylammonium) triiodide.

11. 9 - Ethyl - 9 - thioniaheptadecylenebis (triethylammonium) triiodide.

12. 9:9 - Diethyl - 9 - azoniaheptadecylenebis (triethylammonium) triiodide.

13. 7 - Ethyl - 7 - thioniatridecylenebis (dimethylethylammonium) triiodide.

14. 7 - *n* - Butyl - 7 - thioniatridecylenebis (dimethyl - *n* - butylammonium) triiodide.

15. 7 - Methyl - 7 - thioniatridecylenebis (diethylmethylammonium) triiodide.

16. 7 - *n* - Propyl - 7 - thioniatridecylenebis - (diethyl - *n* - propylammonium) triiodide.

17. 7:7:14:14 - Tetraethyl - 7:14-diazoniaeicosylenebis (triethylammonium) tetraiodide.

18. 11:11:22:22 - Tetraethyl - 11:22-diazoniadotriacontylenebis (triethylammonium) tetraiodide.

19. 11:11:18:18 - Tetraethyl - 11:18-diazoniaoctacosylenebis (triethylammonium) tetraiodide.

20. 7:7:18:18 - Tetraethyl - 7:18-diazoniatetracosylenebis (triethylammonium) tetraiodide.

21. 7:14 - Diethyl - 7:14 - di - *n* - propyl - 7:14 - diazonaeicosylenebis (diethyl - *n* - propylammonium) tetraiodide.

22. 7:7:14:21:21 - Pentaethyl - 7:21-diazonia - 14 - thioniaheptacosylenebis (triethylammonium) pentaiodide.

23. Bis - 5 - diethylaminopentyl sulphide.

24. Bis - (6 - diethylaminohexyl)ethylamine.

25. Bis - (10 - diethylaminodecyl)ethylamine.

26. 1:20 - Bis - (diethylamino) - 7:14-diethyl - 7:14 - diazaeicosane.

27. 1:32 - Bis - (diethylamino) - 11:22-diethyl - 11:22 - diazadotriacontane.

28. Bis - (13 - diethylamino - 7 - ethyl - 7-azatridecyl) Sulphide.

29. Bis - 8 - diethylaminooctyl sulphide.

30. Bis-(8-diethylaminooctyl) ethylamine.

31. 1:28 - Bis - (diethylamino) - 11:18-diethyl - 11:18 - diazaoctacosane.

32. 1:24 - Bis - (diethylamino) - 7:18-diethyl - 7:18 - diazatetracosane.

33. A method of preparing a poly-onium compound substantially in accordance with any of the Examples.

34. A poly-onium compound prepared by any of the methods of claim 34 or its obvious chemical equivalents.

35. The compound claimed in any of claims 1 to 5, in which the anion is the iodide, or bromide, or chloride, or tartrate.

H. D. FITZPATRICK & CO.,

Chartered Patent Agents,

94, Hope Street, Glasgow, C.2, and  
3, Gray's Inn Square, London, W.C.1.

## PROVISIONAL SPECIFICATION

No. 22293 A.D. 1957

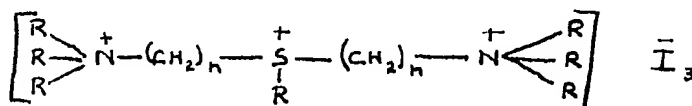
**Poly-Onium Neuromuscular Blocking Agents**

We, NATIONAL RESEARCH DEVELOPMENT CORPORATION, a British Corporation established by Statute, of 1, Tilney Street, London, W.1, do hereby declare this invention to be described in the following statement:—

This invention relates to neuromuscular blocking agents and its object is to provide by synthesis certain tris-onium compounds which

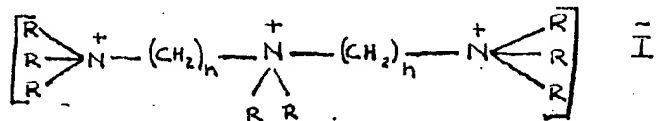
have been found to have properties by virtue of which they are suitable as such agents, acting in some respects like (+)-tubocurarine and decamethonium.

The invention comprises the tris-onium compounds symbolized by the general formula (I):—



in which R is the ethyl radical (Et=C<sub>2</sub>H<sub>5</sub>) or the methyl radical (Me=CH<sub>3</sub>) and in which n is at least 4.

The invention also comprises the tris-onium compounds symbolized by the general formula (II):—



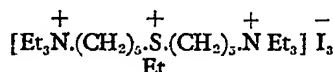
in which again R is the ethyl radical or the methyl radical and n is at least 4.

The invention also comprises methods of producing compounds according to the aforesaid general formulae I and II.

By way of illustration specific compounds representative of the series according to the foregoing general formulae I and II and methods of preparing such compounds will now be described.

**EXAMPLE 1.**

This example is according to general formula I in which R is Et in each instance and n is 5. The specific formula is:—



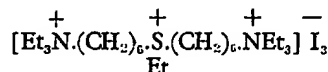
This compound, 1:11 - bis - (triethylammonium) - 6 - ethylthiaundecanonium triiodide, was prepared from 5 - hydroxypentyl-diethylamine (according to Synerholm, *Journal American Chemical Society*, 1947, 69 2581) through the intermediate bis - 5 - diethylaminopentyl sulphide as follows:—

**Bis-5-diethylaminopentyl Sulphide.** Excess thionyl chloride (9 ml.) in benzene (20 ml.) was slowly added to a stirred solution of 5-hydroxypentyl-diethylamine (14.3 g.) in benzene (100 ml.). The yellow crystalline mass obtained on removal of the solvent and excess reagent was dissolved in water (20 ml.); the solution was cooled to 0° C and basified with sodium hydroxide solution (30 ml.; 20%). Extraction with ether, drying (Na<sub>2</sub>SO<sub>4</sub>) and

evaporation of the solvent gave crude 5-chloropentyl-diethylamine (15.9 g.). The latter in ethanol (8 ml.) was slowly added to a hot solution of anhydrous sodium sulphide (4.4 g.) in water (5 ml.) and ethanol (16 ml.), and the mixture was refluxed for 3 hours with continuous stirring. The residual liquid, after removal of the solvent at 100° was poured into brine (50 ml.) and extracted with ether. The ethereal extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated, and the residue was distilled, yielding bis - 5 - diethylaminopentyl sulphide as a pale yellow oil (3.55 g., 25%), b.pt. 200—205° C/1.2 mm. 1:11 - (triethylammonium) - 6 - ethylthiaundecanonium triiodide. Bis - 5 - diethylaminopentyl sulphide (0.85 g.) was refluxed with excess ethyl iodide (4 ml.) for not less than 40 minutes. Removal of excess reagent under reduced pressure and recrystallisation of the product from ethanol gave 1:11 - bis(triethylammonium) - 6 - ethylthiaundecanonium triiodide, m.pt. 136.5—137.5° C.

**EXAMPLE 2.**

This example also is according to general formula I in which R again is Et in each instance and n is 6. The specific formula is:—

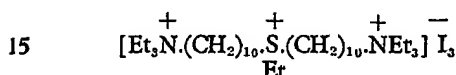


This compound, 1:13 - bis - (triethylammonium) - 7 - ethylthiatridecانونium triiodide, was prepared from bis - 6 - diethylaminohexyl

5 sulphide (according to Edwards and Stenlake, *Journal of Pharmacy and Pharmacology*, 1955, 7, 852) (1.64 g.) by refluxing with ethyl iodide (3 ml.) for 25 mins. Removal of excess reagent under reduced pressure and recrystallisation of the product from ethanol gave almost colourless crystals of 1:13 - bis - (triethylammonium) - 7 - ethylthiatridecanonium triiodide (2.95 g., 76.3%) m.pt. 142—143° C.

#### 10 EXAMPLE 3.

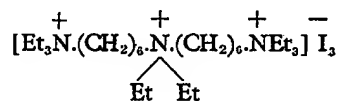
This example also is according to general formula I in which R again is Et in each instance and *n* is 10. The specific formula is:—



20 This compound 1:21 - bis(triethylammonium)-11-ethylthiaheneicosanonium triiodide, was prepared from bis - 10 - diethylaminodecyl sulphide (1.1 g.) (according to Edwards and Stenlake, *Journal of Pharmacy and Pharmacology*, 1955, 7, 852) by refluxing with ethyl iodide (2 ml.) and ethanol (1 ml.) for 45 minutes. Evaporation to dryness under reduced pressure yielded 1:21 bis (triethylammonium) - 11 - ethylthiaheneicosanonium triiodide (0.6 g.) m.p. 123.5—124° C (from acetone-ether).

#### EXAMPLE 4.

30 This example is according to general formula II in which R is Et in each instance and *n* is 6. The specific formula is:—



35 This compound, 1:13 - bis(triethylammonium) - 7 - diethylazatridecanonium triiodide, was prepared from 6 - hydroxyhexyldiethylamine (according to Work, *Journal of the Chemical Society*, 1942, 426; and Edwards and Stenlake, *Journal of Pharmacy and Pharmacology*, 1955, 7, 852) through the intermediate 6-bromohexyldiethylamine, 6-diethylaminohexylethylamine and bis (6-diethylaminohexyl) ethylamine as follows:—

40 6 - Bromohexyldiethylamine. 6 - Hydroxyhexyldiethylamine (19 g.) was refluxed with 48% hydrobromic acid (63 ml.) and concentrated sulphuric acid (8.7 ml.) for 5 hours. The cooled solution, diluted with water (50 ml) was basified with sodium carbonate, and extracted with chloroform. Evaporation of the solvent under reduced pressure at 17° C, and filtration of solid matter from the oily residue gave 6 - bromohexyldiethylamine (15.1 g.) as a reddish brown oil, which was used immediately in the next stage.

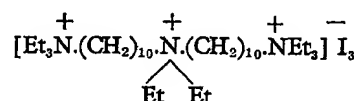
55 6 - Diethylaminohexylethylamine Hydrochloride. Crude 6-bromohexyldiethylamine (15 g.) in chloroform (50 ml.) and excess ethylamine (20 ml.) were refluxed for 1 hour. Evaporation of the chloroform and excess ethylamine, addition of water to the residue and extraction with benzene yielded an oily product which on distillation gave crude 6-diethylaminohexylethylamine (5.4 g.) b.p. 125° C/16 mm. Treatment of the product with dilute hydrochloric acid and evaporation to dryness gave 6 - diethylaminohexylethylamine dihydrochloride, m.p. 172—173° C (from ethanol-ether).

60 Bis - (6 - diethylaminohexyl) ethylamine. Crude 6 - diethylaminohexylethylamine (3.55 g.) was refluxed with 6 - bromohexyldiethylamine (2.2 g.) in chloroform (40 ml.) for  $\frac{3}{4}$  hour, allowed to stand overnight, and the solution evaporated to dryness under reduced pressure. Addition of water to the residue, extraction with benzene, evaporation of the solvent and fractional distillation of the residue gave bis - (6 - diethylaminohexyl) - ethylamine, as an oil (0.43 g.) b.p. 152—153° C/0.4 mm.

75 1:13 - Bis - (triethylammonium) - 7 - diethylazatridecanonium triiodide. Bis - (6 - diethylaminohexyl)ethylamine (0.39 g.) was refluxed with ethyl iodide (3 ml.) for 15 minutes. Evaporation of excess ethyl iodide yielded 1:13 - bis(triethylammonium) - 7 - diethylazatridecanonium triiodide (0.57 g.) m.p. 247—248° C (from ethanol).

#### EXAMPLE 5.

90 This example also is according to general formula II in which R again is Et in each instance and *n* is 10. The specific formula is:—



95 This compound, 1:21 - bis(triethylammonium) - 11 - diethylazaheneicosanonium triiodide, was prepared from 10 - hydroxydecyldiethylamine (according to Schinzel and Benoit, *Bulletin Société Chimie Française*, 1939, 6, 501; and Edwards and Stenlake, *Journal of Pharmacy and Pharmacology*, 1955, 7, 852) through the intermediate 10 - bromodecyldiethylamine, 10 - diethylaminodecylethylamine and bis (10 - diethylaminodecyl) ethylamine as follows:

100 10 - Bromodecyldiethylamine. This intermediate compound was prepared from 10 - hydroxydecyldiethylamine (20.1 g.) by the method described in Example 4 for preparing 6 - bromohexyldiethylamine and was obtained as a colourless oil (21.4 g.) b.p. 130—131° C/0.65 mm.

110 10 - Diethylaminodecylethylamine. 10 - Bromodecyldiethylamine (20.9 g.) and excess

- ethylamine (60 ml.) were refluxed for 2 hours. Distillation of the excess ethylamine, addition of water to the residue and extraction with benzene yielded an oily product which on distillation gave 10 - diethylaminodecylethylamine (14 g.) b.p. 133—135° C/0.8 mm. together with bis - (10 - diethylaminodecyl)-ethylamine (0.9 g.) b.p. 216—217° C/0.75 mm.
- 10 Bis - (10 - diethylaminodecyl)ethylamine. This intermediate compound was prepared from 10 - diethylaminodecylethylamine (7.9 g.) and 10 - bromodecyl-diethylamine (9 g.) as described in Example 4 for preparing bis(6-diethylaminoethyl)-ethylamine and was obtained as a pale yellow oil (3.6 g.) b.p. 216—217° C/0.75 mm.

1:21 - Bis(triethylammonium) - 11 - diethylazaheneicosanonium triiodide. Bis (10-

diethylaminodecyl)ethylamine (0.93 g.) was refluxed with ethyl iodide (2 ml.) and ethanol (1 ml.) for 50 minutes. Evaporation to dryness under reduced pressure yielded 1:21-bis (triethylammonium) - 11 - diethylazaheneicosanonium triiodide (1.7 g.), m.pt. 204° C (from acetone-ether).

In the foregoing, although iodine has been specified throughout as the anion, this element as such is not critical to the activity of each compound as a blocking agent, and therefore there may be substituted any pharmaceutically equivalent anion, for example the bromide, the chloride, or the tartrate.

H. D. FITZPATRICK & CO.,  
Chartered Patent Agents,  
94, Hope Street, Glasgow, C.2, and  
3, Gray's Inn Square, London, W.C.1.

#### PROVISIONAL SPECIFICATION

No. 40388 A.D. 1957

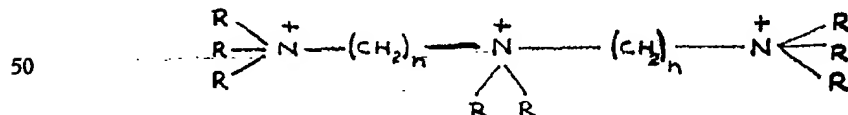
#### Poly-Onium Neuromuscular Blocking Agents

- We, NATIONAL RESEARCH DEVELOPMENT CORPORATION, a British Corporation, established by Statute, of 1, Tilney Street, London, W.1, do hereby declare this invention to be described in the following statement:—

- This invention relates to neuromuscular blocking agents and its object is to provide by synthesis certain poly-onium compounds

which have been found to have properties by virtue of which they are suitable as such agents, acting in some respects like tubocurarine and decamethonium.

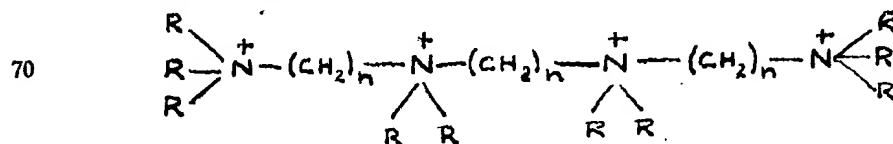
The invention comprises the poly-onium compounds which in their simplest form, namely the tris-quaternary, are symbolized by the general formula (I):—



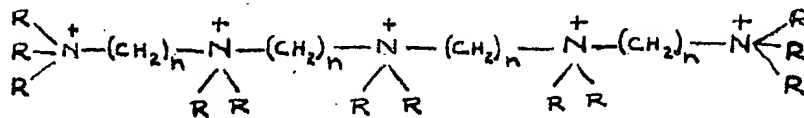
- in combination with an equivalent amount of an anion-providing constituent. In said formula,  $n$  is at least 4 and R is an alkyl radical. The anion-providing constituent is preferably iodine but this element as such is not critical to the activity of each compound as a blocking agent, and therefore there may be substituted any pharmaceutically equivalent anion, for example the bromide, the chloride, or the tartrate. The alkyl radical may be ethyl (Et) but

it may instead be methyl (Me) or it might be propyl, isopropyl, normal butyl, secondary butyl, tertiary butyl or amyl. In any one compound, the alkyl radicals may be the same as or may differ from one another; and  $n$  may have the same or different values.

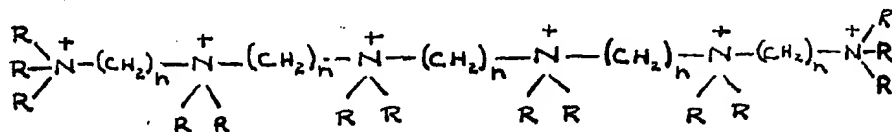
The tetra-quaternary component of the compounds may be symbolized by the general formula (II):—



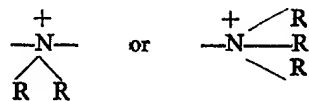
The penta-quaternary component of the compounds may be symbolized by the general formula (III):—



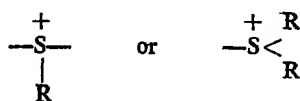
The hexa-quaternary component of the compounds may be symbolized by the general formula (IV):—



In the compounds above depicted, each quaternary component is a quaternary nitrogen group, namely:—



There may be incorporated instead of any one or more of these groups the equivalent tertiary sulphur group, namely:—

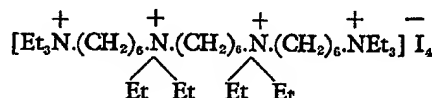


The invention also comprises methods of producing compounds according to the aforesaid general formulae I to IV, each quaternary group being a nitrogen or equivalent sulphur group.

By way of illustration specific compounds representative of the series according to the foregoing general formulae and methods of preparing such compounds will now be described.

#### EXAMPLE 1.

This example is according to general formula II in which in each instance R is Et and n is 6. The specific formula is:—



This compound, 7:7:14:14 - Tetraethyl-7:14 - diazoniaeicosylenebis (triethylammonium) tetraiodide was prepared from 6-hydroxyhexyldiethylamine (according to Work, *Journal of the Chemical Society*, 1942, 426; and Edwards and Stenlake, *Journal of Pharmacy and Pharmacology*, 1955, 7, 852) as follows:—

6 - Bromohexyldiethylamine. 6 - Hydroxyhexyldiethylamine (19 g.) was refluxed with 48% hydrobromic acid (63 ml.) and concentrated sulphuric acid (8.7 ml.) for 5 hours. The cooled solution, diluted with water (50 ml) was basified with sodium carbonate, and extracted with chloroform. Evaporation of the solvent under reduced pressure at 17° C and filtration of solid matter from the oily residue gave 6 - bromohexyldiethylamine (15.1 g.) as a reddish brown oil, which was used immediately in the next stage.

6 - Diethylaminohexylethylamine. Crude 6-bromohexyldiethylamine (15 g.) in chloroform (50 ml.) and excess ethylamine (20 ml.) were refluxed for 1 hour. Evaporation of the chloroform and excess ethylamine, addition of water to the residue and extraction with benzene yielded an oily product which on distillation gave crude 6-diethylaminohexylethylamine (5.4 g) b.p. 125° C/16 mm.

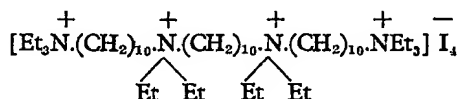
1:20 - Bis (diethylamino) 7:14 - diethyl-7:14 - diazaeicosane Adipic acid (2.54 g.) was refluxed with excess thionyl chloride for 1½ hours. After removal of excess reagent, the

acid chloride was heated in benzene (50 ml.) over a water bath, and an excess of 6-diethylaminohexylethylamine (14.2 g.) in benzene (50 ml.) added with stirring (10 minutes). The mixture was then refluxed gently for 10 minutes, cooled and extracted with 10% hydrochloric acid. The latter solution was basified and extracted with benzene. After removal of solvent, the bulk of the 6-diethylaminohexylethylamine was distilled leaving the crude N,N'-diethyl - N,N'-bis(6 - diethylaminohexyl) - adipamide. Lithium aluminium hydride reduction of this amide in ether, and distillation of the residual oil yielded 1:20-bis - (diethylamino) - 7:14 - diethyl - 7:14-diazaeicosane as a yellow oil (1.15 g., 13%), n<sub>D</sub><sup>20</sup> 1.4695, b.p. 178—185° C./0.25 mm.

7:7:14:14 - Tetraethyl - 7:14 - diazoniaeicosylenebis (triethylammonium) tetraiodide. 1:20 - Bis - (diethylamino) - 7:14-diethyl - 7:14 - diazaeicosane (1.1 g.), ethyl iodide (3 ml.), and ethanol (3 ml.) were refluxed for 20 minutes. Evaporation under reduced pressure and recrystallisation from ethanol yielded 7:7:14:14 - tetraethyl-7:14 - diazoniaeicosylenebis (triethylammonium) tetraiodide (1.1 g., 46.2%), m.p. 239.5—240° C. Found: N, 4.9; I, 45.9 per cent. C<sub>88</sub>H<sub>80</sub>N<sub>4</sub>I<sub>4</sub> requires N, 5.1; I, 45.9 per cent.

#### EXAMPLE 2.

This example also is according to general formula II in which in each instance R again is Et but n is 10. The specific formula is:—



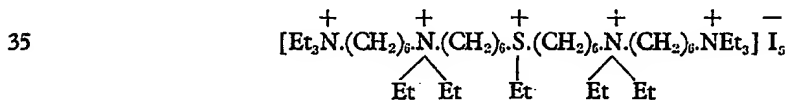
- 11:11:22:22 - Tetraethyl - 11:22 - diazo-  
*niadotriacontylenebis* (triethylammonium)  
 5 tetraiodide was prepared from sebacoyl chloride  
 and 10-diethylaminodecylethylamine as  
 follows:—  
 1:32 - Bis - (diethylamino) - 11:22 - di-  
 ethyl - 11:22 - diazadotriacontane was pre-  
 10 pared from sebacic acid (2.53 g.) and 10-  
 diethylaminodecylethylamine (13.1 g.) as des-  
 cribed for 1:20 - bis - (diethylamino) - 7:14-  
 diethyl - 7:14 - diazaicosane, and was  
 obtained as a yellow oil, b.p. 360—380° (bath)  
 0.7 mm. (4.46 g.; 55%  $n_D^{18}$  1.4692 Found:  
 15 Equiv. (Titration) 165.5  $\text{C}_{32}\text{H}_{90}\text{N}_4$  requires  
 equiv. 162.8.

11:11:22:22 - Tetraethyl - 11:22 - diazo-  
*niadotriacontylenebis* (triethylammonium)

tetraiodide. 1:32 - Bis - (diethylamino)-  
 11:22 - diethyl - 11:22 - diazoniadotriacon-  
 20 tane (0.95 g.) was refluxed with ethyl iodide  
 (3 ml.) and ethanol (3 ml.) for 50 minutes.  
 Evaporation under reduced pressure and  
 recrystallisation from acetone-ether gave  
 11:11:22:22 - tetraethyl - 11:22 - diazo-  
 25 niadotriacontylenebis (triethylammonium)  
 tetraiodide, m.p. 186—187° (1.4 g.; 75.3%)  
 Found: C. 46.8; H. 8.5; I. 39.4 per cent.  
 $\text{C}_{30}\text{H}_{110}\text{I}_4\text{N}_4$  requires C, 47.1; H, 8.7; I, 39.8  
 30 per cent.

### EXAMPLE 3.

This example is according to general for-  
 mula III in which in each instance R again  
 is Et and  $n$  is 6. The specific formula is:—



- 7:7:14:21:21 - Pentaethyl - 7:21 - diazo-  
 mia - 14 - thioniaheptacosylenebis (triethyl-  
 ammonium) pentaiodide was prepared from  
 40 ethyl hydrogen adipate and 6-diethylamino-  
 hexylethylamine as follows:—  
 Ethyl N - ethyl - N - (6 - diethylamino-  
 hexyl) - adipamate. Ethyl adipoyl chloride,  
 prepared by refluxing ethyl hydrogen adipate  
 (20.32 g.) with thionyl chloride in the usual  
 45 way, was dissolved in benzene (60 ml.). 6-  
 Diethylaminohexylethylamine (23.8 g.) in ben-  
 zene (60 ml.) was added slowly (40 mins.) with  
 stirring, and the mixture refluxed gently for  
 15 minutes. After extraction with 10%  
 50 hydrochloric acid, basifying and extraction  
 with benzene, fractional distillation yielded  
 ethyl N - ethyl - N - (6 - diethylaminohexyl)-  
 adipamate as a yellow oil; b.p. 190—200°  
 C./ 0.65 mm.,  $n_D^{17.5}$  1.4630, (16.43 g.;  
 55 39.5%).  
 13 - Diethylamino - 7 - ethyl - 7 - azatri-  
 decan - 1 - ol. Ethyl N - ethyl - N - (6-  
 diethylaminohexyl) - adipamate (16.2 g.) in  
 dry ether (40 ml.) was added to a stirred and  
 refluxing suspension of lithium aluminium  
 60 hydride (14 g.) in dry ether (300 ml.) at a  
 rate sufficient just to maintain refluxing. The  
 reaction mixture was cooled, and water added  
 dropwise to decompose the excess lithium  
 65 aluminium hydride, and then excess water  
 added. The ethereal layer was decanted and  
 the residue washed with ether. The combined  
 ethereal solutions, were dried ( $\text{Na}_2\text{SO}_4$ )  
 evaporated and the residue distilled to yield  
 70 13 - diethylamino - 7 - ethyl - 7 - azatridecan-  
 1-ol, as a colourless oil, b.p. 162—164°  
 C./0.3 mm.,  $n_D^{15}$  1.4717 (7.56 g.; 55%).

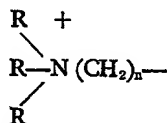
13 - Diethylamino - 7 - ethyl - 7 - azatri-  
 decyl Chloride. 13 - Diethylamino - 7 - ethyl-  
 7 - azatridecan - 1 - ol (7.53 g.) in benzene  
 (20 ml.) was treated with thionyl chloride (5  
 ml.) in benzene (10 ml.). The crystalline mass  
 obtained on removal of the solvent and excess  
 reagent was dissolved in water (10 ml.), the  
 solution cooled to 0° and basified with sodium  
 hydroxide solution. Extraction with ether,  
 drying ( $\text{Na}_2\text{SO}_4$ ), evaporation of the solvent  
 and distillation gave 13 - diethylamino - 7-  
 ethyl - 7 - azatridecyl chloride as a pale yellow  
 oil, b.p. 140—148°/0.2 mm.  $n_D^{17}$  1.4670 (5.7  
 85 g.; 71%).

Bis (13 - diethylamino - 7 - ethyl - 7 - aza-  
 tridecyl) Sulphide was prepared from 13-di-  
 ethylamino - 7 - ethyl - 7 - azatridecyl  
 chloride (5.65 g.) and anhydrous sodium sul-  
 90 phide as described for bis - 5 - diethylamino-  
 pentyl sulphide (according to Edwards, Lewis,  
 Stenlake, Zoha; *Journal of Pharmacy and*  
*Pharmacology*, 1957, Vol. 9, page 1004). Bis-  
 (13 - diethylamino - 7 - ethyl - 7 - azatri-  
 95 decyl) sulphide was obtained as a pale yellow  
 oil, b.p. 300—310° (bath)/0.33 mm.,  $n_D^{12.5}$   
 1.4855, (1.38 g.; 26%)

7:7:14:21:21 - Pentaethyl - 7:21-  
 diazomia - 14 - thioniaheptacosylenebis (tri-  
 ethylammonium) pentaiodide. Bis - (13 - di-  
 ethylamino - 7 - ethyl - 7 - azatridecyl) sul-  
 100 phide (0.24 g.) was refluxed with ethyl iodide  
 (1 ml.) and ethanol (2 ml.) for 20 minutes.  
 Evaporation under reduced pressure and  
 re-crystallisation of the product from acetone-  
 ether yielded 7:7:14:21:21 - pentaethyl-  
 7:21 - diazomia - 14 - thioniaheptacosylene-  
 105 bis (triethylammonium) pentaiodide, m.p.

149—150° (decomp.) (0.12 g.; 22%) Found:  
I, 46.2 per cent.  $C_{46}H_{103}I_5N_4S$  requires I,  
46.0 per cent.

- 5 In the foregoing specification the poly-  
quaternary compounds as symbolized by the  
formulae I, II, III and IV, R is stated to  
represent an alkyl radical. Instead, in any one  
or more instances, R may be an  $\omega$ -trialkyl-  
ammoniumalkyl group, namely:—



10

H. D. FITZPATRICK & CO.,  
Chartered Patent Agents,  
94, Hope Street, Glasgow, C.2, and  
3, Gray's Inn Square, London, W.C.1.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1962.  
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which  
copies may be obtained.